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GUEST EDITORIAL

Prostate Cancer Facts and Fiction

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It is interesting that controversy should exist in the detection and the treatment of the most common major cancer and the second leading killer of men in the United States [1]. Up until 1985, there were few changes in either the incidence or the mortality; however, since that time, several new diagnostic procedures and improvements in treatment have occurred. In 1986, transrectal ultrasound (TRUS) became popular, which permitted the visualization of the prostate and the identification of hypoechoeic areas of possible cancer as well as providing a guide for biopsying. A new spring-loaded biopsy gun permitted painless transrectal biopsies in the office. The introduction of prostate specific antigen (PSA) blood test doubled the detection rate and quadrupled the number of radical prostatectomies [2]. Concerns were voiced about (1) the possible detection of occult or latent carcinomas that are known from autopsy studies [3,4] to exist in 30% of normal men over the age of 50, (2) the argument that men with localized cancers of the prostate do just as well untreated as treated [5–9], and (3) the commonly held opinion that prostate cancer in older men is more benign than in younger men and that most die of other causes.

Two principles must be met in a successful screening program. First, there must be a test or procedure that can detect cancers earlier. And second, earlier treatment must have a better outcome. In prostate cancer screening the tests were mainly PSA in combination with a digital rectal examination (DRE). Numerous studies [10–13] have been done to determine the performance of these tests, which in general, show that PSA will double the detection rate compared to DRE. PSA detects about 70% but misses about 30% of cancers that are detected by the DRE. The tests are complementary. They must be able to create lead time, to reach out into the future, and detect cancers in asymptomatic individuals. Lead time is the estimate of how many years it might reach into the future. It can be estimated in serial screening studies or trials by measuring the number of cases detected in the initial (prevalence) screening divided by the number of cases detected in the second annual screen or in a control group. Three prostate screening studies [14–16] have all shown increases of two to four times the initial expected detection rates, and then in subsequent screens the detection rates were much lower. The majority of the cancers detected were confined to the prostate and amenable to curative treatment. Advanced cancers were rarely found in subsequent screening rounds.

Because the sharp rise in prostate cancer incidence was associated with a screening test, one should examine the expected dynamics of cancer screening. (a) The first suggestion of a benefit is the detection of a large number of cancers in the initial screen as compared to the incidence or to subsequent screens. (b) The second indication is a shift in stage with the major increase in earlier stages and a decrease in advanced stages. The initial screen generally detects both the prevalent early as well as advanced cancers. In subsequent examinations few advanced cancers should be detected. (c) The third indication is an increase in survival rates. However, because of possible lead time biases or length biases, survival may be misleading. (d) The fourth and best indicator of success is a decrease in deaths from prostate cancer. Because deaths are most forcibly influenced by those with advanced disease at diagnosis, an absolute decrease in the rate of advanced disease generally heralds a decrease in mortality.

Earlier detection must be linked to more effective treatment to achieve a decline in mortality. If treatment or lack of treatment fails to alter the course of the disease, and the patient dies at the same time as without screening, it is known as lead time bias. Survival time is increased without an increase in longevity. A second bias of concern in screening studies is known as length bias sampling because of the possibility of detecting indolent slow-growing cancers that may never have surfaced in life. It is known that with increasing age microscopic foci of cancerous appearing cells are found in autopsy series in about 30% of men over 50 years of age. In a study of men with bladder cancer treated by total cystoprostatectomy occult cancers were found in 40%, and 8% of them

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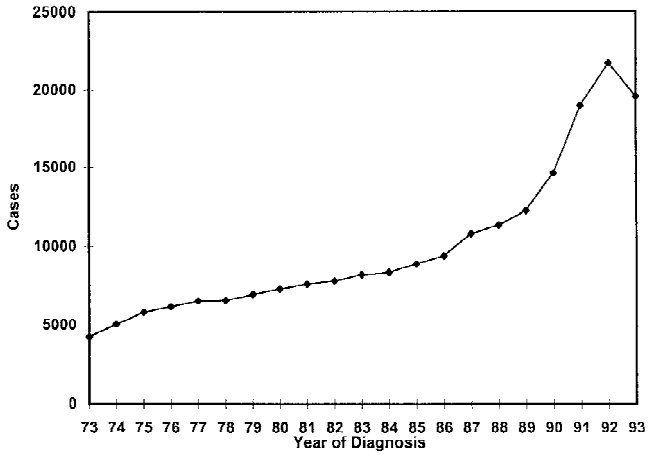

Fig. 1. Prostate cancer (n = 208,234) diagnosed in the Surveillance Epidemiology and End-Results (SEER) program of the National Cancer Institute, 1973–1993. (Unpublished data for 1994 shows a continued decline.)

were large enough to be of clinical importance. Occult carcinomas have been characterized as being microfocal, well-differentiated, and under 0.2–0.3 cm in volume [10–15]. Clinically important cancers of the prostate may be palpable, are histologically grade 2, 3, or 4 (moderately to poorly or undifferentiated), and are larger than 0.5 cm in size. The aggressiveness of a prostate cancer is related to both its grade, volume, and PSA level. It has been reported that about 16% of the cancers detected through PSA screening are compatible with length bias sampling. In the past, these cancers were frequently detected on a transuretheral resection for benign prostatic hyperplasia and were generally not otherwise treated.

These issues will be addressed utilizing the 208,234 prostate cancers diagnosed from 1973–1993 in nine population based registries of the Surveillance Epidemiology and End-Results (SEER) program of the National Cancer Institute which monitors cancer in the United States.

Increased Incidence Then Decrease

After PSA was introduced in the late 1980s, a rapid increase in incidence during 1988–1993 occurred. It reached its zenith in 1992, then began to decline in 1993–1994 (Fig. 1; the data for 1994 are unpublished and are not shown). Preliminary unpublished data for 1995 and 1996 show a continuing decline to baseline rates. In a screening study, the dates of initial and subsequent screenings are known, thus making possible the calculation of initial and subsequent screening detection rates and estimates of lead time. However, in the SEER data it is unknown when screening occurred. In the prostate patterns of care studies of the American College of Surgeons in 1986 only 7.6% were detected by PSA, while in 1990, it was 70%. Similarly, population based health surveys have shown that 48% of men over 40 years of age and 73% of men over 65 years of age have had a PSA within the past year. Therefore, in the SEER database one can assume that a certain percentage of initial examinations occurred in year 1989, some in 1990, others in 1991 and 1992, etc. If one were to assume a baseline incidence of 82 (as it was in 1982) and the peak rate of 186 (as it was in 1992), then the lead time must be greater than 2.3 years = 186/82. From published descriptive studies it appears that lead time estimates vary from 2 to 4 years, meaning that at the initial screen many more cases are detected than expected. When the majority of the population at risk have had an initial examination, then subsequent examinations having a much smaller yield result in a decrease in incidence. Undoubtedly, there has also been a decrease in screening because of negative publicity.

A Shift in Stage and Grade

The major increase was in those with early-stage disease with a decrease in the rate and crude number of patients detected with advanced disease as expected in screening (Fig. 2). The generalized historical stages of in situ, localized, regional, and distant disease were utilized, because it allowed 21-year stage trends with few of unknown stage; the modified American Joint Committee (AJC) stage, generated from a computer algorithm, was only available from 1988 to 1993 and had an unacceptably high percentage of unknown stage. Although an increase in early stage is anticipated, the more important group are those with distant stage disease. They will progress to death from prostate cancer unless they die beforehand of something else. A decrease in the rate or actual number of patients with advanced disease is the most reliable predictor of a decrease in mortality rate.

In prostate cancer, in particular, the histologic grade is clinically useful in measuring more accurately the aggressiveness of the cancer. In the SEER program, grade was redefined in 1982 to encompass Gleason's scores (1–3 were included in grade 1, 4–6 in grade 2, 7–8 as grade 3, 9–10 as grade 4). Therefore, trends in grade are particularly important after 1982. The major increase was in histologic grade 2 (Gleason's 4, 5, and 6) cancers which are generally considered to be of clinical importance rather than in grade 1 (Gleason's 1–3) frequently found in occult or latent carcinomas (Fig. 3).

Note: frequency counts or rates/100,000/year in defined populations are used to avoid the problem of percentage migration. When using percentages and there is a large increase in early cases, automatically there is an apparent reduction in the percentage with distant disease (even though in actual fact there may no change in the actual number of those with distant disease).

Increases in Survival

Changes in survival are shown in Figure 4 where an 8-year relative survival interval was chosen to span the

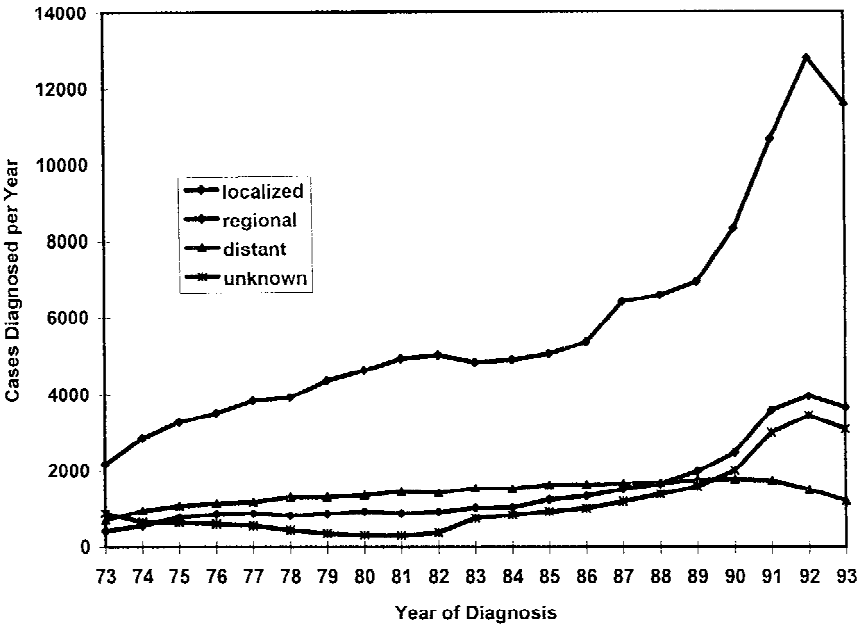

Fig. 2. Crude stage trends in prostate cancer, 1973–1993.

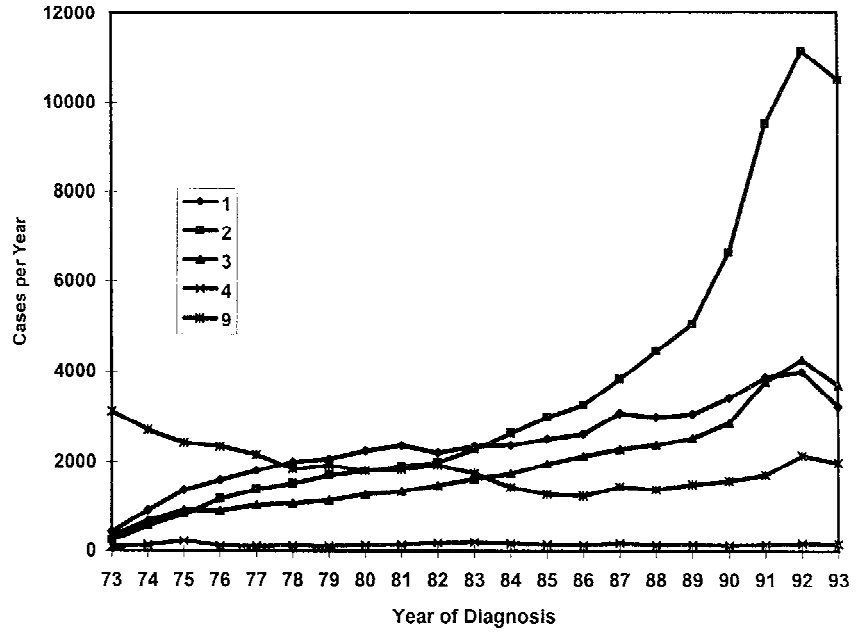

Fig. 3. Trends in the grade of prostate cancer, 1973–1993.

years 1985 to 1993 and to contrast with the period 1973 to 1980 when no screening was being done. There was a 20% increase in relative survival. Survival by stages are reflected in three progressive time periods (Table I). Localized and regional disease survivals show marked improvements, but little change was seen in the survival of those with distant stage. Regional stage is frequently a result of operating on what was thought to be organ confined cancer, but at operation or on the pathology report the cancer is found to have penetrated through the prostatic capsule and into the surrounding tissues. Thus, clinically it was localized but pathologically it turns out to be regional with a slight decrease in the relative survival.

Changes in Treatment

The second principle of screening is that earlier treatment must have a better outcome. With an influx of early cases detected through screening, particularly in prostate

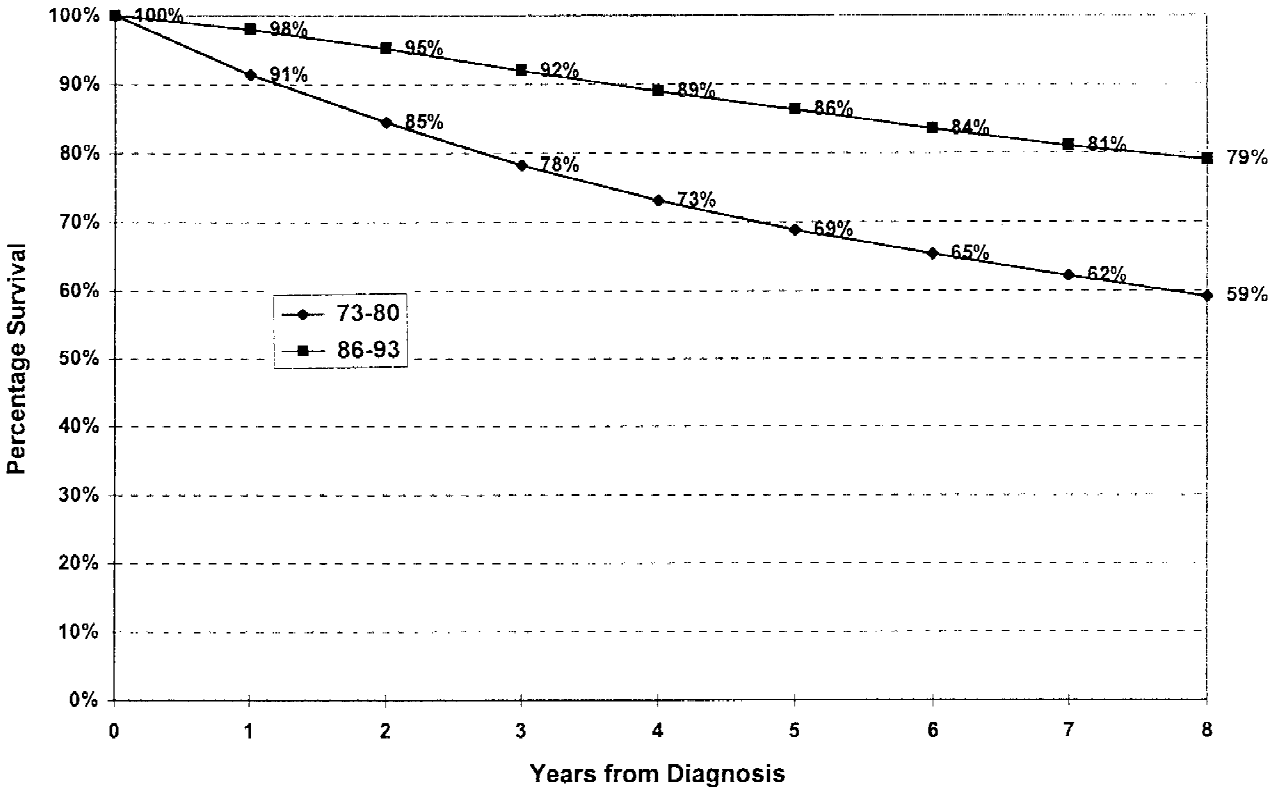

Fig. 4. Eight-year relative survival rates for prostate cancer, 1973–1980 and 1986–1993.

cancer with the possibility of detecting occult disease, one cannot be sure how much lead time bias or length bias may be playing a role in increasing survival rates. Best treatment cannot be determined in the SEER data by comparing survival rates because of selection bias as well as possible lead time bias and length bias. Most often we are not comparing the effects of treatment as much as selection (Fig. 5, Table II). In the analysis of the 26% (27,467 patients), treated by radical prostatectomy, the relative survival rate was over 100% because the patients were healthier than the average men in the normal population of that age without cancer. When corrected for death from other causes it rounded off at 100% at 10 years. The survival rates for radiation therapy was only 78% at 6 years, and other therapy showed a 30% survival at 5 years. This is partially explained by the stage distribution by treatment modalities. In the group treated by radical prostatectomy, only 1% had distant disease, where as 9% in the radiation group and 23% of those who had other treatment had a distant disease (Table II). In analyzing all patients dying of prostate cancer, 41% had distant disease at the time of diagnosis, 32% had localized, and 14% had regional disease. Also, in the group treated by radical prostatectomy 15% is found with grade 1 cancers which, in the absence of further information, is compatible with clinically unimportant or occult disease.

TABLE I. 5-Year Relative Survival Rates for Prostate Cancer for Various Time Periods

	1973–1977	1983–1987	1988–1993
Localized	80.0	93.0	99.1
Regional	70.2	82.2	93.6
Distant	27.5	29.2	30.7

Causes of Death

The average age of these patients with prostate cancer was 72 years, the same as the life expectancy of men in the U.S. This means that half of the normal men will die by age 72. Prostate cancer is vying with comorbidity for the death of the patient. Because a patient dies of a heart attack does not mean that he would not have died of prostate cancer had he lived longer, nor does it mean that his cancer is any less virulent. In analyzing the 208,234 cases of prostate cancer from 1973 to 1993 with excellent follow-up through 1995, with death certificates on all the deaths, one can determine the likely cause of death (Table III). It showed that 38% died of prostate cancer and 62% died of other causes. In analyzing deaths by age groups, as you might expect, the older the patients, the more likely they were to die. At the upper limit of 85 plus years of age, 70% died of other causes and 30% died of prostate cancer (Table IV).

TABLE II. Prostate Cancer (PCA) 1973–1993*

	PCA deaths[a]		Radical[b]		Radiation		Other treatments	
Localized	12,687	32%	16,659	55%	35,749	61%	45,125	53%
Regional	5,671	14%	11,750	39%	10,894	19%	5,820	7%
Distant	16,244	41%	161	1%	5,391	9%	19,276	23%
Unknown	4,552	12%	1,442	5%	6,737	11%	14,520	17%
	39,173	100%	30,017	100%	58,790	100%	84,941	100%

*Data from SEER Program Public Use Tape 1973–1993 February 1996.
[a]Death from prostate cancer stated on the death certificate.
[b]Radical prostatectomy.

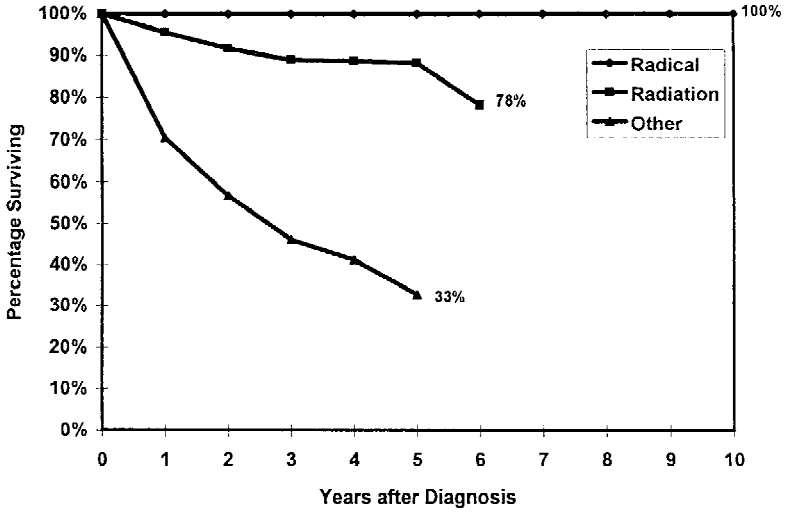

Fig. 5. Prostate cancer by treatment modality (selection bias).

TABLE III. Prostate Cancer (PCA) by 1995 Vital Status and Cause of Death

Year Diagnosed	Total	Alive	Dead	Cause of death PCA (%)		Other %
1973	4,250	213	4,037	1,636	41	59
1974	5,041	293	4,748	1,873	39	61
1975	5,816	444	5,372	2,053	38	62
1976	6,164	531	5,633	2,187	39	61
1977	6,523	699	5,824	2,145	37	63
1978	6,571	835	5,736	2,171	38	62
1979	6,959	979	5,980	2,185	37	63
1980	7,282	1,181	6,101	2,216	36	64
1981	7,618	1,476	6,142	2,246	37	63
1982	7,814	1,747	6,067	2,291	38	62
1983	8,222	2,144	6,078	2,200	36	64
1984	8,358	2,581	5,777	2,128	37	63
1985	8,899	3,160	5,739	2,234	39	61
1986	9,392	3,888	5,504	2,105	38	62
1987	10,818	5,258	5,560	2,168	39	61
1988	11,340	6,403	4,937	1,896	38	62
1989	12,274	7,810	4,464	1,754	39	61
1990	14,615	10,514	4,101	1,538	38	62
1991	19,007	15,640	3,367	1,206	36	64
1992	21,723	19,581	2,142	682	32	68
1993	19,548	18,732	816	259	32	68
Totals	20,8234	104,109	104,125	39,173	38	62

TABLE IV. SEER Prostate Cancer Dead of All Causes

	1973–1992				
	Total	Dead of other causes		Dead of prostate cancer	
40–44	91	31	34%	60	66%
45–49	332	118	36%	214	64%
50–54	1,293	525	41%	768	59%
55–59	4,092	1,881	46%	2,211	54%
60–64	9,196	4,761	52%	4,435	48%
65–69	15,934	9,273	58%	6,661	42%
70–74	20,944	13,010	62%	7,934	38%
75–79	21,593	14,278	66%	7,315	34%
80–84	17,125	11,679	68%	5,446	32%
85 +	13,492	9,377	70%	4,115	30%
	104,092	64,933	62%	39,159	38%

Prostate Cancer Deaths in Older Men

A decrease in deaths from prostate cancer is the ultimate goal of screening. To really measure this goal one must separate those that die of other causes from those that die of prostate cancer. Correcting for age and comorbidity using relative survival rates or considering only deaths from prostate cancer (the two methods are

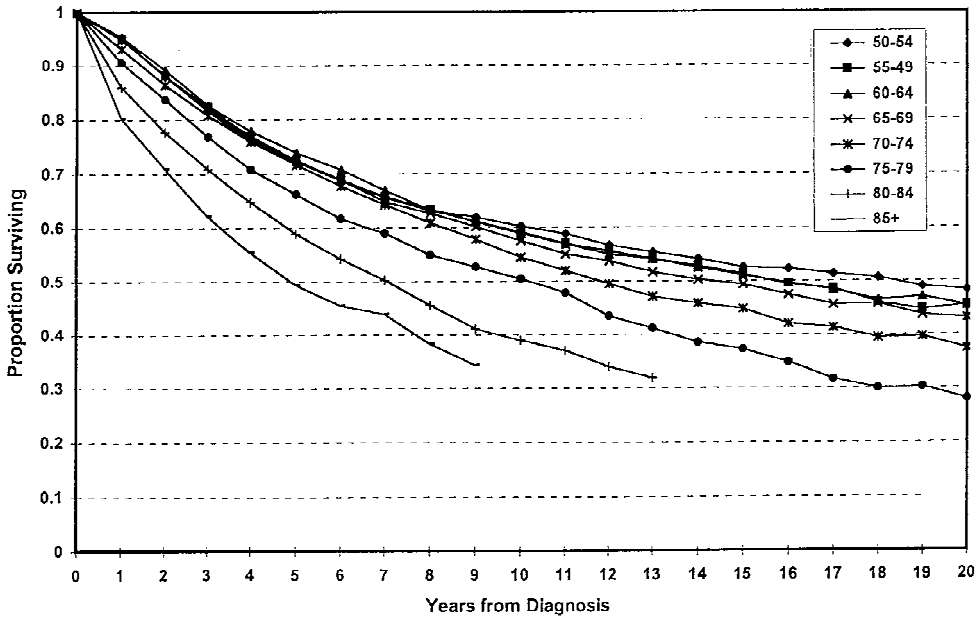

Fig. 6. Prostate cancer: 20-year relative survival rate by age group.

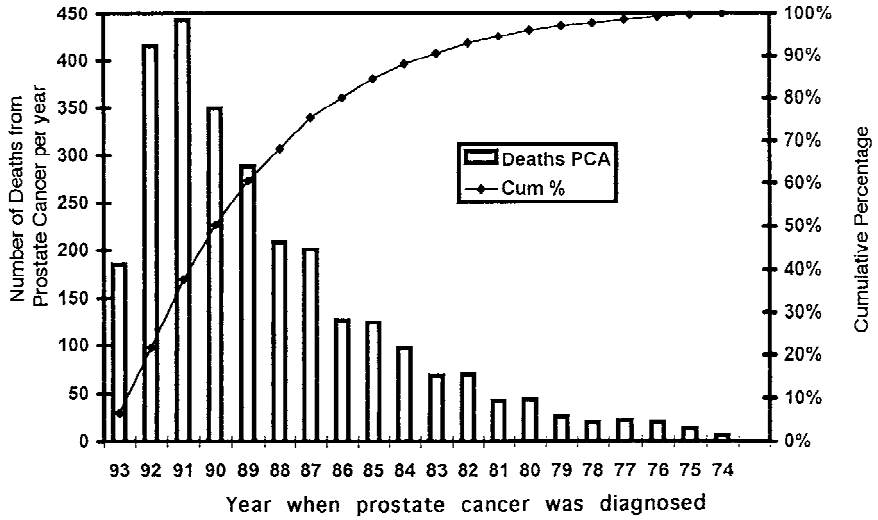

Fig. 7. Mortality from prostate cancer, 1993 (deaths in 1993), by year of diagnosis. (PCA: prostate cancer; cum: cumulative).

equivalent), the 20-year survival rates were similar for ages 50–69 but were about 6% poorer for men aged 70–74 and 16% poorer for men 75–79; those 80–84 years old have a 32% rate at 13 years and for those 85+ a 35% 9-year rate (Fig. 6). The distant stage for men 75 years of age and older was 16% compared to 13% for under 75 and grade 4 (Gleason's 9 and 10) were 13% in the older and 8% in the younger group. There were few (5.4%) 75 to 79 years of age and 0.7% 80 years or over, treated by radical prostatectomy, suggesting that older men with prostate cancer do not have less but more aggressive cancers or that their treatment is less effective.

Changes in Mortality

How long does it take to change mortality? Figure 7 shows all deaths from prostate cancer (death certificate) *dying* in the year 1993 (as in mortality rates) by year of diagnosis going back 20 years. Sixty-one percent were diagnosed within 5 years and 88% within 10 years of their deaths from prostate cancer. A similar result is reached utilizing the cohort diagnosed in 1974 and determining the percentage of deaths from prostate cancer occurring in each year of follow-up over the next 20 years: 66% died within 5 years and 89% within 10 years.

Over the time of generalized screening for prostate cancer in the U.S., 1989–1993, there has been a decrease in the diagnosis of distant disease as noted in Figure 2. This decrease began in 1992 and became more pronounced in 1993 and in unpublished data from 1994. In November 1996, a preliminary report from the National Center for Health Statistics noted a 6.3% decrease in the United States mortality rate for prostate cancer between 1991 and 1995.

SUMMARY

1. The observed increase in prostate cancer incidence followed by a decrease, was not an epidemic, but the result of generalized prostate cancer screening in the United States.
2. The increase showed a shift in stage, to mainly early disease in grade 2 (Gleason's 4–6) clinically significant cancers with a decrease in advanced disease.
3. There was an increase in the use of radical prostatectomy, mainly in men 40 to 75 years of age with a 10-year relative survival rate of 100%. It appears that 15% were grade 1 cancers and in the absence of more information may have been clinically unimportant.
4. There was a 20% increase in the overall relative survival rate for prostate cancer.
5. There was a decrease in the incidence of advanced disease followed by a 6.3% decrease in the United States mortality rate for prostate cancer.
6. It appears that an annual PSA blood test and a DRE on all men over 50 years of age followed by appropriate treatment has decreased deaths from prostate cancer.

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